

Immunomorphological assessment of regional lymph nodes for predicting metastases in oral squamous cell carcinoma

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ABSTRACT

Background: Oral squamous cell carcinoma is the most common neoplasm and comprises of approximately 80% of the cancers occurring in the oral cavity. The role of the host response to this neoplasm has been recognized, and for many years the regional lymph node in tumor-bearing hosts has been considered as an anatomic barrier to the systematic dissemination of tumor cells. Morphological evaluation of the regional nodes has aided in understanding the immune response.

Aim: The current study was carried out to observe the morphological changes occurring in the regional lymph nodes and to evaluate whether these features could be helpful in assessing the immunological status of the patient, and thereby, the prognosis of the patient.

Materials and Methods: The study was based on lymph nodes from 63 patients with oral squamous cell carcinoma, who underwent radical neck dissection or modified neck dissection. In the lymph node, four morphological patterns were observed that included lymphocyte predominance, germinal center predominance, mixed pattern (sinus Histiocytosis), and an unstimulated pattern. The cases were then divided into four groups according to the predominant immunoreactivity pattern based on the World Health Organization (WHO) standardized system for reporting human lymph node morphology.

Results: Revealed that risk of metastases to cervical lymph nodes in patients with lymphocyte predominance was less (28.6%) when compared to the high risk of metastases with germinal center predominance (68%), and these results were statistically significant ($P < 0.05$). Patients with a mixed pattern showed less risk of metastases (45.4%), while those with an unstimulated pattern had increased risk of metastases (66.6%), but the results were not statistically significant. It was also found that in the positive nodes, germinal center hyperplasia (50.2%) was the predominant pattern.

Conclusion: The present study revealed that patients with lymphocyte predominance had less risk of metastases and patients with germinal center predominance had a high risk of metastases to the lymph node.

Key words: Germinal center predominance, lymph node, lymphocyte predominance, metastases, mixed pattern (sinus histiocytosis), oral squamous cell carcinoma, unstimulated pattern

Received : 15-09-10
Review completed : 02-05-11
Accepted : 08-11-11

Malignant neoplasms are major causes of fear, morbidity, and mortality all over the world. The term 'Oral Cancer' is used to describe any malignancy that arises from oral tissues. Globally,

Oral cancer is the sixth most common cancer. In developing countries like India, it is a major public health problem accounting for 40% of all malignancies.^[1,2] Squamous cell carcinoma is the most common cancer representing 90 to 95% of all malignancies occurring in the oral cavity. It is defined as the, "malignant epithelial neoplasm exhibiting squamous differentiation, characterized by the formation of keratin and the presence of intercellular bridges".^[3] It accounts for 3% of all cancers in men and 2% in women. It ranks sixth among the most common cancers in men and the twelfth in women. The current male:female ratio is approximately 1.8:1.^[1]

Prognosis of patients with oral squamous cell carcinoma is difficult to predict, despite the diagnosis and therapeutic progress in the field of oncology. Even now, half of the

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Access this article online	
Quick Response Code:	Website: www.ijdr.in
	DOI: 10.4103/0970-9290.99059

patients afflicted, will die within the first two years of diagnosis. There are various factors that influence prognosis, such as, patient factors (age, sex, etc.) and tumor factors (size, site, histopathological grade, and metastases). Among all these factors the development of lymphatic metastases is considered as the single most important factor influencing the outcome of the patient with oral squamous cell carcinoma. The five-year survival rate of patients with squamous cell carcinoma of the upper digestive tract is reduced by almost 50% with the development of cervical metastases.^[4]

Immune responses to these malignant neoplastic lesions have been well-documented. Ever-growing evidence exists, which supports the concept of a close relationship between the host immunological defense status and prognosis for various types of malignant neoplastic disease. Even though the intimate mechanism of interaction between the host immune system and tumors have yet to be more thoroughly understood, many studies have been performed to correlate the immunological status with prognosis.^[5-7] In most of the *in vitro* studies, circulating blood lymphocytes were used as test cells.^[8] It is, however, conceivable that immune response may be recognized more clearly in structures close to the tumor, such as, in the proper tumor itself or in the draining lymph nodes.

Lymph node morphology does reflect certain parameters of immune responses associated with humoral antibody production or cell-mediated immunity, as the lymph node is one of the tissues most frequently examined by histopathologists. Correlation between the lymph node immune response and other parameters such as site, size, and histopathological grade of the primary tumor, could assist the physicians in their final assessment and treatment planning for the patient.

There are studies on the clinical and histological features of the primary tumor and its metastases to lymph nodes, but very few studies have been conducted to know other concurrent changes occurring in the lymph nodes due to metastases. The present study has been conducted to review the cases of radical neck dissections and study in detail the architectural changes occurring in the lymph node, with and without metastases. Our present study seems especially interesting as head and neck cancer is known to be associated with early deficiencies of cell-mediated immunity; and, as with other malignancies, these cell-mediated immunodeficiencies correlate with the recurrence of the malignancy.^[9] It may be assumed that the histological analysis of the regional tumor-draining lymph nodes could elucidate the immunological host-tumor relationship and render additional information on patient survival.

MATERIALS AND METHODS

The study was based on 63 excision biopsy specimens of oral squamous cell carcinoma, of patients who had undergone radical neck dissection or modified neck dissection. These

tissue specimens were fixed in 10% formalin, routinely processed and paraffin blocks prepared. Tissue sections of five to six micron thickness were obtained using a soft tissue microtome and were stained with Hematoxylin and Eosin. A minimum of three sections were taken from each lymph node at different levels and observed by two independent observers, and then a conclusion was drawn on the predominant histopathological pattern.

The number of nodes available for each case selected for the study ranged from 10 to 60. The total number of lymph nodes examined was 1795, with a mean of 27.6 per patient. Out of this total lymph node, 171 were positive nodes, which showed the presence of metastatic foci and the remaining 1624 lymph nodes showed no evidence of metastases. Lymph nodes evaluated for the study were from the submental and submandibular (Level I), upper jugular (Level II), mid jugular (Level III), lower jugular (Level IV), and the posterior triangle (Level V).

To assess patient immune response in the regional lymph nodes the criteria used to classify all lymph nodes were in agreement with a previous proposal for a standardized system of reporting human lymph node morphological characteristics in relation to immunological function.^[9-11]

The World Health Organization proposal for a standardized system of reporting human lymph node morphology in relation to immune reaction^[9]

Lymphocyte predominance [Figure 1]

The lymph nodes are enlarged with an increased number of small lymphocytes throughout the paracortex (T cell Zone). The lymphoid follicles are effaced and the germinal centers mostly unapparent. The expanded paracortex showed an increased number of pyroninophilic cells, hyperplasia or reticular cells, and prominent endothelial cells in the capillaries.

Germinal center predominance [Figure 2]

The lymph nodes are similarly enlarged, but the increase in volume is caused by hyperplasia of the follicles, particularly the germinal centers. The germinal centers are prominent and composed mostly of large, primitive cells, with basophilic cytoplasm, tangible body macrophages, and numerous mitoses. The medullary cords are also enlarged and contain increased numbers of plasma cells. Sinus Histiocytosis may coexist with these changes.

Mixed pattern (predominantly sinus histiocytosis) [Figure 3]

A predominance of sinuses characterizes this morphological pattern, which can occur in isolation or together with one of the preceding patterns. The lymph nodes are enlarged by markedly distended sinuses and hyperplasia of the sinus histiocytes. The pale staining of the histiocytes and endothelial cells, which line the branching lumina, contrasts strongly with the dark staining of the lymphocytic areas and produces the characteristic appearance of sinus histiocytosis.

Unstimulated pattern [Figure 4]

The entire cortex is thin, showing no germinal centers, the deep cortex is hypocellular showing no expansion or activity, and the medullary cords are unremarkable.

Depending on the predominant pattern the cases were then classified into four groups. For a great majority of cases, most or all the lymph nodes from an individual patient showed the same type of reaction pattern. Only infrequently did several lymph nodes of an individual patient show substantial evidence of more than one type of reaction pattern. When this did occur, however, a predominant pattern was readily discernible.

In addition each lymph node was evaluated for any evidence of metastatic foci.

The positive nodes showed three types of morphological patterns, they are:

Total replacement [Figure 5]

Metastases + germinal center predominance: [Figure 6]

Metastases + lymphocyte predominance: [Figure 7].

The results were statistically analyzed using the Chi-square test.

$$X^2 = \frac{\sum(O - E)^2}{E}$$

O = observed value

E = expected value

Chances of micro metastases cannot be completely ruled out. In our study we did, to the best of our knowledge and ability, subject each lymph node to three different sections at various levels, and whenever in doubt, we took additional sections to come to the exact conclusion as to which the predominant pattern was. The level I to level V groups of lymph nodes were analyzed for any metastatic foci. Unless the great bulk of a lymph node was replaced by a metastatic tumor, no serious difficulty arose in evaluating a lymph node with metastases for its morphological pattern of response as well as for its predominant histomorphological pattern

RESULTS

The present study was done to observe the morphological changes occurring in lymph nodes in patients with oral squamous cell carcinoma, and to evaluate whether

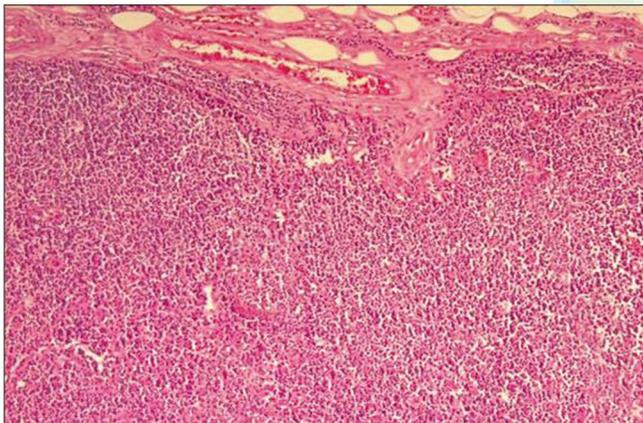


Figure 1: Lymphocyte predominance

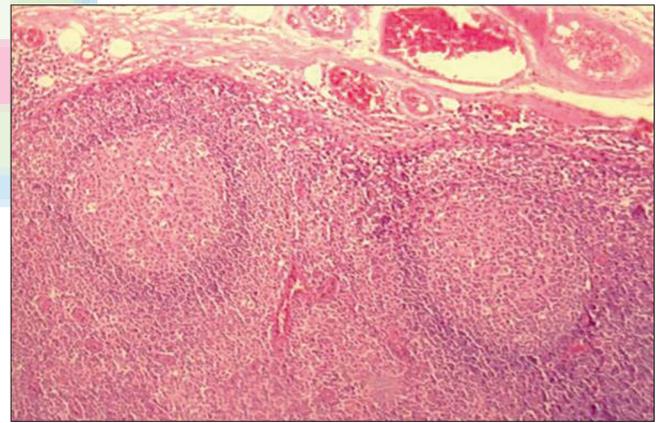


Figure 2: Germinal center predominance

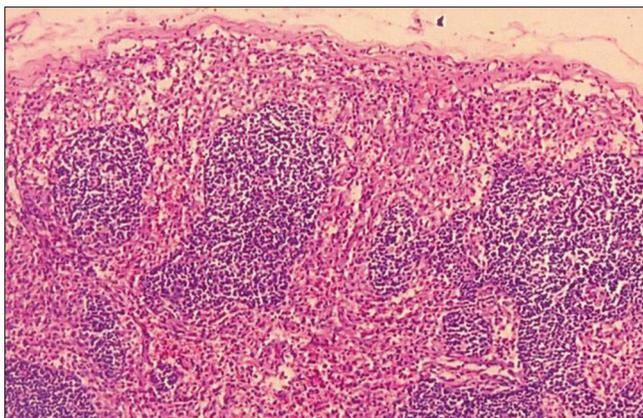


Figure 3: Mixed pattern (sinus histiocytosis)

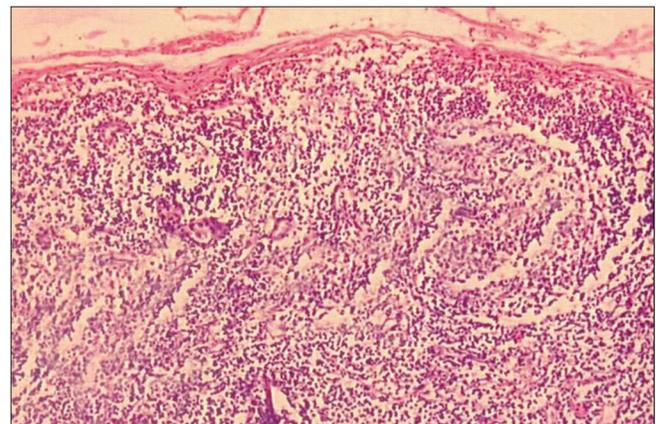


Figure 4: Unstimulated pattern

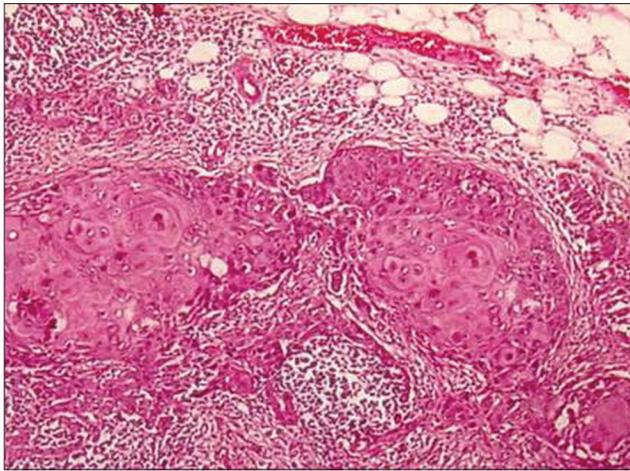


Figure 5: Total replacement

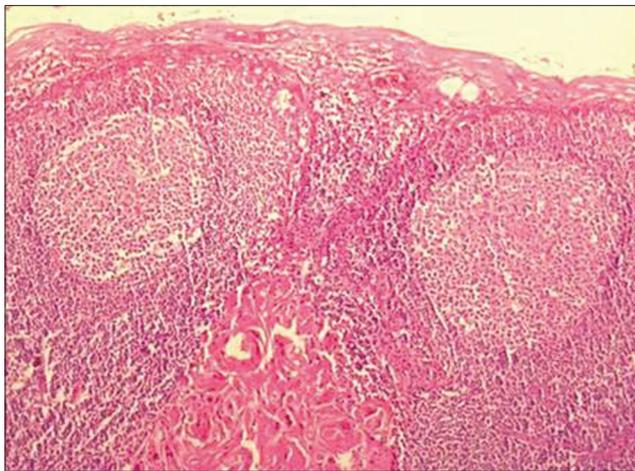


Figure 6: Metastases with germinal center predominance

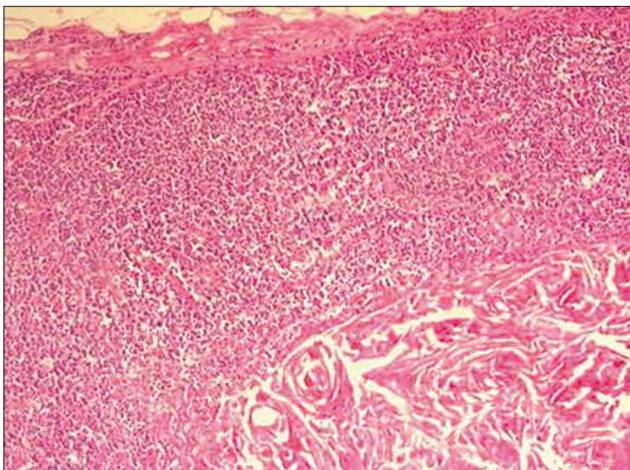


Figure 7: Metastases with lymphocyte predominance

these features could be helpful in assessing the immunomorphological status of the patient and thereby the prognosis of the patient.

A total of 1795 lymph nodes were harvested from 63 cases and were observed for the presence or absence of metastases, and it was found that 32 cases showed evidence of metastases and 31 had no evidence of metastases to the cervical lymph nodes. Out of 1795 lymph nodes 171 (9.5%) showed the presence of metastases and 1624 (90.5%) showed no evidence of metastases.

All the cases were divided into four different groups according to the locoregional lymph node immunoreactivity. The predominant pattern was usually discernible. The 63 patients were grouped as follows; [Table 1].

Relation of metastases to a predominant lymph node histological pattern

A correlation was made between the predominant histological pattern and presence or absence of metastases [Table 2]. Out of 21 cases with the lymphocyte predominance pattern, metastases was seen in only six cases when compared to 15 cases in which metastases was not seen. This difference was statistically significant ($P < 0.05$); inferring that a patient with a lymphocyte predominant pattern had less chance of metastases. Similarly out of 25 cases with germinal center predominance, metastases were seen in 17 cases when compared to eight cases with no metastases. This difference was also statistically significant ($P < 0.05$), and we could infer that the patient with germinal center predominance had a slightly higher chance of metastases. Out of 11 cases with a mixed pattern, metastases were seen only in five cases when compared to six non-metastatic cases. This difference was not statistically significant. Out of six cases with an unstimulated pattern, metastases were noted in four cases and two cases had no metastases. Although this difference was not statistically significant, from the study we could conclude that a patient with an unstimulated pattern had a slightly higher chance (66%) of metastases.

Relation of the predominant lymph node histological pattern and positive nodes

Analyzing a predominant lymph node pattern in 171 positive lymph nodes, we observed that 57 nodes (33.3%) showed total replacement, 86 nodes (50.2%) showed germinal center predominance, and 28 nodes (16.5%) showed a mixed pattern. From this we could observe that the germinal center predominance pattern predominates in the positive nodes.

Table 1: Patients categorized according to the predominant lymph node histological pattern

Predominant pattern	Cases
Lymphocyte predominance [Figure 1]	21
Germinal center predominance [Figure 2]	25
Mixed pattern (sinus histiocytosis) [Figure 3]	11
Unstimulated [Figure 4]	06
Total	63

Table 2: Relation of metastases to predominant lymph node histological pattern

Pattern	Number	Metastases (%)	Non metastases (%)	X ²	P
Lymphocyte predominance	21	6 (28.6)	15 (71.4)	6.22	0.02, S
Germinal center predominance	25	17 (68)	8 (32)	5.86	0.02, S
Mixed pattern (sinus histiocytosis)	11	5 (45.4)	6 (54.6)	0.08	0.84, NS
Unstimulated	06	4 (66.6)	2 (33.4)	0.81	0.37, NS
Total	63	32	31		

Table 3: Size of primary tumor versus predominant lymph node pattern

Pattern	Total	<4 cm (%)	4–6 cm (%)	>6 cm (%)
LP	21	11 (52.3)	9 (42.8)	1 (4.9)
GCP	25	10 (40)	12 (48)	3 (12)
MP	11	4 (36.3)	5 (45.4)	2 (18.3)
US	6	3 (50)	2 (33.4)	1 (16.6)
Total	63	28	28	7

Table 4: Size of the primary tumor versus metastases

Size	No	Metastases (%)	Non metastases (%)
<4 cm	28	11 (39.3)	17 (60.7)
4–6 cm	28	16 (57.1)	12 (42.9)
>6 cm	7	5 (71.4)	2 (28.6)
Total	63	32	31

Relation of the size of the primary tumor versus predominant lymph node pattern

Correlation was done between a predominant lymph node pattern and the size of the primary tumor [Table 3]. It was found that with tumor sizes of: <4 cm, 4–6 cm, and >6 cm, lymphocyte predominant patterns of 52.3, 42.8, and 4.9%; germinal center predominance patterns of 40, 48, and 12%; mixed patterns of 36.3, 45.4, and 18.3%; and unstimulated patterns of 50, 33.4, and 16.6%, respectively, were noted. Correlating the lymph node predominant pattern with the size of the primary tumor did not give any significant result.

Relation of the size of the primary tumor versus metastases

Correlation was done between the size of the primary lesion and the presence or absence of metastases [Table 4]. It was found that when the size of the lesion was <4 cm, the chances of metastases was 39.3%, when size of lesion was between 4 and 6 cm, the chances of metastases was 57.1%, and when lesion exceeded 6 cm, the chances of metastases was 71.4%, suggesting a direct proportion of the lesion size to the metastases.

DISCUSSION

Squamous cell carcinoma is the most common neoplasm and comprises of approximately 80% of the cancers occurring in the oral cavity. Despite optimal treatment, the prognosis of the advanced squamous cell carcinoma remains poor. This poor survival is primarily due to a high rate of locoregional failure and secondarily to distant metastases or some other malignancy. Incidence of regional lymph node metastases in head and neck cancer is high and the presence of lymph

node metastases is the single most important prognostic factor.^[12,13] An understanding of the mechanism whereby tumor cells are prevented from developing lymph node metastases and of tumor establishing the metastases, is crucial for tumor biology.^[13] The unpredictable clinical behavior of patients with malignant disease has led many investigators to search for factors that may be used as an index of prognosis. As a result, the concepts of clinical staging and histological grading of the primary tumor have evolved and are employed in the routine evaluation of patients with a wide variety of tumors. Even as the stage and grade of the primary neoplasm have been shown to have prognostic significance, the biological variability of individual patients has led investigators to search for other factors that might refine the clinician’s ability to predict survival.^[14]

The role of the host defense mechanism against tumor growth is gaining increased attention in clinical as well as experimental studies. Regional lymph nodes are considered to have their primary function not merely in the anatomic barriers to the systematic dissemination of tumor cells, but also in the immunological surveillance.^[15] Available evidence indicates that responses that appear to be immunologically mediated in the host may play a role in the achievement of long-term survival. The immune response can be assessed histologically in the draining lymph nodes. The morphological and immunological patterns are lymphocyte predominance and sinus histiocytosis, which supposedly reflect the active response of the thymus-dependent cells linked to cellular immunity. Germinal center predominance, indicates an active response in the thymus-independent germinal centers related to humoral immunity. The morphological change indicated that unstimulated lymphocyte depletion is a paucity of lymphocytes in the nodes.^[16] Although analysis of the histological lymph node reactivity has been studied in various types of cancers occurring in the breast, larynx, lungs, stomach, and uterine cervix,^[10,14,17-21] few studies have focused on head and neck cancer.^[9,12,16,22]

Therefore, the present study was conducted to observe the morphological changes occurring in the lymph nodes, to correlate these changes with the presence or absence of metastases. Our study seemed especially interesting, as head and neck cancer was known to be associated with early deficiencies of cell-mediated immunity. The study included lymph nodes from 63 patients, of oral squamous cell carcinoma. The draining lymph node showed four

histological patterns, which were classified as lymphocyte predominance, germinal center predominance, mixed pattern (sinus histiocytosis), and the unstimulated pattern. Our results suggested that these histological patterns could be useful in determining metastases.

When a correlation was done with the histology of the predominant lymph node pattern for the presence or absence of metastasis, it was found that metastases to the cervical lymph node occurred twice more frequently in patients showing germinal center predominance (17/25 or 68%) than in patients with lymphocyte predominance pattern (6/21 or 28.6%), which showed a statistically significant difference ($P < 0.05$) and the same results were observed by Tsakralides V *et al.*, in their study on patients with cervical and breast cancer^[10,23] and by Di Giorgio A *et al.*, in their study on lung carcinoma.^[20] In contrast Berlinger NT *et al.*, in their study on patients with head and neck carcinoma found that both germinal cell predominance and the lymphocyte predominant pattern experienced less incidence of metastases, 23 and 31%, respectively. This was attributed to the evidence of concomitant lymphoblastic activity in the thymus-dependent deep cortex.^[9]

In patients with mixed pattern (sinus histiocytosis) metastases occurred in 5/11 or 45.4%. This result was not statistically significant. A lower percentage of metastases associated with mixed pattern in our study correlated with other studies done by Silverberg SG *et al.*, in mammary carcinoma,^[17] Tosi P *et al.*, in lung carcinoma^[19] and Patt BS in laryngeal carcinoma^[24].

In patients with the unstimulated pattern metastases occurred in 4/6 or 66.4%. This result was not statistically significant due to less number of cases with the unstimulated pattern. Higher percentage of metastases associated with the unstimulated pattern, in our study, correlated with the studies done on cervical and breast cancer by Tsakralides V *et al.*^[10,23] and in head and neck cancer by Berlinger *et al.*^[9]

Di Giorgio A hypothesized that, “cellular immune activity may prevent lymph node invasion, whereas, humoral response may facilitate metastases” in patients with lung carcinoma.^[19] This hypothesis was supported by other studies by Tosi *et al.* in bronchogenic carcinoma^[19] and Hunter *et al.* in mammary carcinoma.^[25] In our study it was found that humoral immunity, as evidenced by germinal center predominance, facilitated nodal invasion, and so, the above-mentioned theory could be applied to squamous cell carcinoma occurring in the oral cavity. The relation between the development of a humoral response and lymph node metastatic growth remains unclear. Nevertheless, the appearance of a humoral immune response seems to favor the metastatic spread through the lymph nodes by block or inhibition of the histiocytes

and T-lymphocyte cytotoxic activity, (cellular response against tumor cells).^[20]

In most of the studies lymph node immunoreactivity was correlated with survival of the patient, but we could not correlate this factor in our study, as there was no consistent follow-up of the patients. In patients with the lymphocyte predominance pattern and sinus histiocytosis, both reflected changes related to cellular immunity and had better prognosis and longer survival.^[10,19,22,25,26] In a majority of the studies, germinal center predominance, which reflected changes in humoral immunity, had an unfavorable prognosis and a shorter survival time.^[10,19,22,25,26] However, few studies showed that germinal center predominance was associated with better prognosis and longer survival.^[9,16,18,20] The unstimulated pattern was always associated with poor prognosis and shorter survival rate.^[9,10,14,25]

Berlinger *et al.*,^[9] explains the question, ‘why a person should manifest no morphologically demonstrable response in the regional nodes to the tumor challenge, which demands direct analysis?’ One possibility is that the tumor is only very weakly antigenic. It may be that weak antigenicity could be insufficient at times even to stimulate the draining regional nodes. However, Takasugi and co-workers have demonstrated, by using a microssay for cell-mediated immunity, the specific reactivity of lymph nodes from patients with head and neck squamous cell carcinoma against cultured squamous carcinoma cells derived from patients with head, and neck squamous cell carcinoma against cultured squamous carcinoma cells derived from laryngeal tumors. It seems possible that in some way it can exert an influence that generates a defective immune response not only in the regional lymph nodes, but also in one that is more widely excised.

In a study done by Tosi *et al.*^[19] and Giorgio *et al.*,^[20] the positive nodes of bronchogenic carcinoma and lung carcinoma were analyzed and it was found that the germinal center predominance pattern was seen at a higher percentage in the positive nodes. In our study we analyzed the positive nodes at all levels and found three types of reaction patterns; total replacement 35%, germinal center predominance 48%, and mixed response 17%, among the 171 positive nodes. We also found that in the positive nodes germinal center predominance was seen at a higher percentage. These findings confirmed the fact that germinal center hyperplasia was associated with lymph node neoplastic invasion.

The size of the primary tumor was correlated with the predominant lymph node morphological pattern and no statically significant results were obtained. Di Giorgio in his study on lung carcinoma patients found that a lesion greater than 4.2 cm (57.5%), had a brisk humoral response, whereas, most patients with a smaller lesion (53.9%) had

lymph nodes with poorly developed cortical areas and germinal centers.^[20] The author enumerates these features to support the hypothesis that the progressive growth of a primary tumor leads to necrosis, worsening anaplasia, and cytolysis, with shedding of high quantities of soluble tumor antigens. These antigens are capable of stimulating humoral reactivity and blocking the cytotoxic action of T-cells, thus improving the malignant spread.^[27,28]

The risk of nodal metastases correlates with the size of the primary tumor. Smaller tumors have a relatively lower incidence of metastatic spread to the lymph nodes, as compared to larger tumors.^[4] Lindberg *et al.*, found an increased incidence of lymphatic metastases with the advancing T stage.^[29] In our study also we found that the size of the primary tumor was directly proportional to the percentage of metastases, although the results were not statically significant.

Barnes summarized the relation of oral squamous cell carcinoma and TNM staging to the five-year survival rate and found that stage I was 85%, stage II was 66%, Stage III was 41% and stage IV was 9%.^[2] In our study, all the patients who underwent surgery belonged to either stage III or Stage IV. Metastasis in stage III was less 9/22 or 40.9%, when compared to stage IV 24/41 or 58.5%, and this result was not statistically significant ($P>0.05$). Analysis of the lymph node pattern in these two stages showed no correlation between the disease stage and the lymph node immunomorphological pattern. A similar type of observation was also made by Di Giorgia *et al.*, in lung cancer patients.^[20] Although we did not find any difference between stage IV and stage III, we observed that stage IV patients had a slightly higher percentage of germinal center predominance, and unstimulated and mixed pattern of lymph nodes. Further studies have to be undertaken to correlate this change with cases in stage I and stage II, to make conclusions.

CONCLUSION

The present study revealed that patients with lymphocyte predominance had less risk of metastases to the lymph node and patients with germinal center predominance had a high risk of metastases to the lymph node. Although the other patterns did not show statistically significant results, we could conclude that the mixed pattern had less chance and the unstimulated pattern had a high chance of metastases to the lymph nodes.

Conventional methods of examining the lymph node in oral squamous cell carcinoma include only the presence or absence of metastases, however, results of this study highlight the status of the immune system, which in turn, is related to the prognosis of the patient. It would be prudent to include the immunomorphological evaluation of the lymph node on a routine basis, which would give a fair idea

to the pathologist, to report to the referring surgeon, for a comprehensive treatment protocol.

The current study appears to be of significant value in predicting metastases. However, this is a unicentric approach, and hence, further studies including a multicentric approach, for example, use of immunostaining will ensure 100% results in predicting the predominant lymph node pattern, and thereby, metastasis. Therefore, this study along with *immunohistochemistry* (IHC) would have helped us to come to a more authoritative evidence-based concept.

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How to cite this article: Yadav ST, Madhu Shankari GS, Chatura K, Dhanuja RJ, Rashmi M. Immunomorphological assessment of regional lymph nodes for predicting metastases in oral squamous cell carcinoma. *Indian J Dent Res* 2012;23:121-2.

Source of Support: Nil, **Conflict of Interest:** None declared.

